Review

Defective implantation and placentation: laying the blueprint for pregnancy complications

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Abstract

Normal implantation and placentation is critical for pregnancy success. Many pregnancy-related complications that present late in gestation (such as pre-eclampsia and preterm labour) appear to have their origins early in pregnancy with abnormalities in implantation and placentation. Implantation is characterized by invasion of the maternal tissues of the uterus by fetal trophoblast, and the degree to which trophoblast invades these tissues appears to be a major determinant of pregnancy outcome. Excessive invasion can lead to abnormally firm attachment of the placenta to the myometrium (placenta accreta) with increased maternal and perinatal morbidity. Inadequate invasion, specifically restricted endovascular invasion, has been implicated in the pathophysiology of such conditions as pre-eclampsia (gestational proteinuric hypertension), preterm premature rupture of membranes, preterm labour, and intrauterine growth restriction. The molecular and cellular mechanisms responsible for implantation remain enigmatic. This review will include an overview of implantation followed by a discussion of a number of molecular mechanisms implicated in defective implantation and placentation including the role of decidual prostaglandins and haemorrhage in regulating trophoblast invasion. An improved understanding of the molecular mechanisms responsible for abnormal implantation and placentation will likely improve clinicians’ abilities to treat disorders that occur along this continuum, including infertility, recurrent pregnancy loss, pre-eclampsia, and preterm birth.

Keywords: human, implantation, placenta, pre-eclampsia, pregnancy, preterm labour

Introduction

Human reproduction entails a fundamental paradox: although critical to the survival of the species, many aspects are relatively inefficient and wastage appears excessive. Fecundity (the probability of pregnancy occurring within one menstrual cycle) peaks at around 30% (Zinaman et al., 1996; Hoozemans et al., 2004) and only 50–60% of all conceptions advance beyond 20 weeks of gestation (Wilcox et al., 1988). Of those lost, 75% fail to implant and are not recognized clinically (Wilcox et al., 1988). Normal implantation and placentation is thus critical for a successful pregnancy. Many pregnancy-related complications that present late in gestation (such as pre-eclampsia and preterm labour) appear to have their origins early in pregnancy with abnormalities in implantation and placentation. Implantation is characterized by invasion of the maternal tissues of the uterus by fetal trophoblast, and the degree to which trophoblast invades the decidualized endometrium (decidua) and inner third of the myometrium appears to be a major determinant of pregnancy outcome. Inadequate invasion, specifically restricted endovascular invasion, has been implicated in the pathophysiology of such conditions as pre-eclampsia (gestational proteinuric hypertension), preterm premature rupture of membranes, preterm labour, and intrauterine growth restriction. The molecular and cellular mechanisms responsible for implantation remain enigmatic. This review will include an overview of implantation followed by a discussion of a number of molecular mechanisms implicated in defective implantation and placentation including the role of decidual prostaglandins and haemorrhage in regulating trophoblast invasion.
Normal implantation and placentation

Very few specimens exist to document the first weeks of human embryonic development, and ethical controversy limits the use of human embryos generated for research purposes. Much understanding of early human development is therefore inferred from animal studies. The initial stages of pre-implantation development, from fertilized ovum (zygote) to a solid mass of cells (morula), occur as the embryo transits the Fallopian tube. The morula reaches the uterine cavity 2–3 days after fertilization. Implantation occurs around days 6–7 post-conception. Analogous to events in several primate species (Pijnenborg et al., 1981b; Enders and Lopata, 1999) human implantation probably includes three stages. Initial adhesion of the blastocyst to the uterine wall (apposition) is unstable. Microvilli on the apical surface of syncytiotrophoblasts interdigitate with microprotrusions (pinopodes) on the apical surface of the luminal epithelium. The next stage, stable adhesion, is characterized by increased physical interaction between the trophectoderm and the uterine luminal epithelium. Shortly thereafter, invasion begins and syncytiotrophoblasts penetrate the uterine epithelium. By day 10 post-conception, the blastocyst is completely embedded in subepithelial stromal tissue and the uterine epithelium grows to cover the implantation site (Bensirschke et al., 1991). Thereafter, mononuclear cytotrophoblasts stream out of the trophoblastic shell to invade the entire endometrium and inner third of the myometrium (interstitial invasion) (Pijnenborg et al., 1981a) as well as the maternal uterine vasculature (endovascular invasion) (Pijnenborg et al., 1981b). The latter process, which begins the process of placentation, establishes the definitive uteroplacental circulation and places fetal trophoblast in direct contact with maternal blood.

Regulation of trophoblast invasion

Complications that present relatively late in pregnancy (such as pre-eclampsia and preterm labour) appear to reflect errors that occur much earlier in placental development. Cytotrophoblast invasion to the proper depth is a major factor in determining pregnancy outcome. Excessive invasion resulting from a failure of the maternal tissues to restrain the invading cytotrophoblast cells (Hoozemans et al., 2004) can lead to an abnormally firm attachment of the placenta to the myometrium (placenta accreta), extension into the myometrium (placenta increta), or invasion through the myometrium into adjacent organs (placenta percreta). Despite improvements in diagnosis and management, these disorders are still associated with significant maternal morbidity and mortality, primarily due to haemorrhage.

Inadequate invasion has been implicated in the pathophysiology of pre-eclampsia. Pre-eclampsia (gestational proteinuric hypertension) is the leading cause of maternal mortality in the industrialized world and increases perinatal mortality five-fold. Although the aetiology of pre-eclampsia is unknown, the characteristic pathological lesion is variably shallow interstitial cytotrophoblast invasion and, more consistently, restricted endovascular invasion (Brosens, 1977; Meekins et al., 1994; Zhou et al., 1997; Redman and Sargent, 2005). In pre-eclampsia, cytotrophoblasts that invade uterine vessels fail to switch their adhesion molecule repertoire to resemble that of vascular cells (Zhou et al., 1997). Thus, the uterine arterioles remain as small-bore, high-resistance vessels that cannot adequately respond to the ever-increasing demands of the fetoplacental unit for blood flow. The end result is progressive uteroplacental insufficiency with release of an as yet unidentified ‘toxaemic factor’ from the dysfunctional (ischaemic) placenta that damages the vasculature throughout the mother’s body leading to widespread vascular injury and increased capillary permeability (Roberts et al., 1989), the pathophysiological hallmark of pre-eclampsia. Although restricted endovascular invasion of the placenta was first identified in association with pre-eclampsia, it now seems clear that it is also associated with other pregnancy complications including miscarriage, preterm labour, pPROM, and IUGR (Kim et al., 2003; Ozturk et al., 2004).

Successful implantation is the end result of a complex molecular dialogue between a receptive, hormonally primed uterus and a mature, activated blastocyst. Although the molecular and cellular mechanisms responsible for implantation are not well understood, it is clear that multiple signals are needed to synchronize blastocyst maturation and uterine receptivity, including sex steroid and peptide hormones, growth factors, cytokines, and immunological factors (summarized in Tables 1 and 2 respectively) (Figure 1) (see Jauniaux, 2000; Norwitz et al., 2001; and Hoozemans et al., 2004 for review). Abnormalities in one or more of these factors can lead to pregnancy failure (spontaneous abortion) or defective implantation with resultant downstream clinical complications (such as pre-eclampsia or preterm labour). Although many losses involve genetic abnormalities (Simpson, 1980), there is often no known cause. It is beyond the scope of this review to address all of the factors implicated in defective implantation and placentation, but the role of decidual prostaglandins and haemorrhage in regulating trophoblast invasion with be discussed further.

Role of prostaglandins in implantation and placentation

Concentrations of endogenous prostaglandins in human decidua are lower in early pregnancy than in the endometrium at any stage of the menstrual cycle (Maathuis et al., 1978; Abel et al., 1980; Norwitz, 2000), due primarily to a decrease in prostaglandin synthesis and not increased metabolism (Norwitz and Wilson, 2000). The administration of exogenous prostaglandins, intravenously, intra-amniotically or vaginally, in all species examined and at any stage of gestation induces abortion. Moreover, an inability to suppress decidual prostaglandin production around the time of implantation has been associated with early pregnancy loss (Abel et al., 1980; Jaschevatzky et al., 1983). Taken together, these data suggest that pregnancy is maintained by a mechanism that tonically suppresses uterine prostaglandin synthesis throughout gestation. Since endometrial prostaglandin production is down-regulated also in ectopic pregnancy (Abel et al., 1980), it seems likely that systemic rather than local mediators are involved. The most likely candidate for this regulation is progesterone.

Progesterone receptor antagonists such as RU 486 readily induce abortion if given before 7 weeks of gestation (Peyron et al., 1993). Similarly, surgical removal of the corpus luteum, the source of progesterone in the first trimester, results in
Table 1. Uterine (maternal) factors associated with implantation and early pregnancy maintenance*. Numbers in square brackets indicate numbered reference shown in footnote.

| Factor                                      | Suggested role                                                                 | Type of evidence | Quality of evidence
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Cytokines/growth factors</strong></td>
<td></td>
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</tr>
<tr>
<td>Interleukin-1 [1–4]</td>
<td>Facilitates cross-talk between the blastocyst and uterus, promotes endometrial proliferation and differentiation, and regulates endometrial angiogenesis and vascular permeability</td>
<td>Animal data only</td>
<td>A</td>
</tr>
<tr>
<td>Interleukin-2 [1]</td>
<td></td>
<td>Animal data only</td>
<td>B</td>
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<tr>
<td>Leukaemia inhibiting factor [1, 5–8]</td>
<td></td>
<td>Animal data, in-vitro</td>
<td>A</td>
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<tr>
<td>Insulin-like growth factor I and II [1, 9]</td>
<td></td>
<td>Animal data only</td>
<td>B</td>
</tr>
<tr>
<td>Colostrum stimulating factor [1, 10]</td>
<td></td>
<td>Animal data only</td>
<td>C</td>
</tr>
<tr>
<td>Transforming growth factor and β [1, 11, 12]</td>
<td></td>
<td>Animal data only</td>
<td>C</td>
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<tr>
<td>Hepatocyte growth factor [1, 13–16]</td>
<td></td>
<td>Animal data only</td>
<td>C</td>
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<tr>
<td>Fibroblast growth factor [1, 17]</td>
<td></td>
<td>Animal data only</td>
<td>C</td>
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<tr>
<td>Heparan-binding epidermal growth factor [18–22]</td>
<td></td>
<td>Animal data only</td>
<td>C</td>
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<tr>
<td>Oestradiol-17 17β [24]</td>
<td></td>
<td>Animal data, in-vitro</td>
<td>A</td>
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<tr>
<td>Steroid hormones</td>
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<tr>
<td>Oestradiol-17β [24]</td>
<td>Proliferation and differentiation of uterine epithelial cells</td>
<td>Animal data, in-vitro</td>
<td>A</td>
</tr>
<tr>
<td>Progesterone [25, 26]</td>
<td>Proliferation and differentiation of endometrial stromal cells</td>
<td>Animal data, in-vitro</td>
<td>A</td>
</tr>
<tr>
<td>Catecholeostrogens [27]</td>
<td>An oestrogen metabolite that activates the blastocyst in preparation for implantation</td>
<td>Animal data only</td>
<td>C</td>
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<tr>
<td><strong>Immuno logistical factors</strong></td>
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<tr>
<td>Interleukin 10 [28]</td>
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<tr>
<td>Indoleamine 2,3-dioxynogenase [29, 30]</td>
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<tr>
<td>Cry (compliment regulator) [31]</td>
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<tr>
<td>Changes in luminal epithelium</td>
<td></td>
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<tr>
<td>Pinopodes [32, 33]</td>
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<td>Muc-1 [34]</td>
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<td>Glycodelin [35]</td>
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<td>Integrin-α,β [36–38]</td>
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<td>Calcinion [39]</td>
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<td><strong>Transcription factors</strong></td>
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<tr>
<td>Mash-2 [40, 41]</td>
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<tr>
<td>Hand-1 [40, 41]</td>
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<td>Inhibitors of DNA binding proteins (ids) [40–42]</td>
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<tr>
<td>Octamer transcription factor-4 (oct-4) [40, 41, 43]</td>
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<tr>
<td>Oestrogen receptor-related receptor-β [40, 41]</td>
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<tr>
<td>Peroxosome proliferator activated receptor-δ [44, 45]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other factors</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hoxa-10 and 11 [46–48]</td>
<td></td>
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<tr>
<td>Cyclooxy-genase-2 [49–54]</td>
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<tr>
<td>Oxygen tension [55]</td>
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</table>

*This table highlights the most important factors and is not intended to be all inclusive.

*Studies were reviewed, evaluated for quality based on the highest level of evidence found in the data, and graded into the following categories: (A) there is good evidence to support involvement; (B) there is fair evidence to support involvement; (C) there is insufficient objective evidence to support involvement; however, involvement has been suggested by respected authorities or anecdotal (unpublished) data.

Table 2. Blastocyst (fetal) factors associated with implantation and early pregnancy maintenance. Values in square brackets indicate numbered reference shown in footnote.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Suggested role</th>
<th>Type of evidence</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytokines/growth factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin 1 [1–4]</td>
<td>Facilitates cross-talk between the blastocyst and uterus, may promote trophoblast differentiation and invasion</td>
<td>Animal data only</td>
<td>A</td>
</tr>
<tr>
<td>Interleukin 6 [1]</td>
<td></td>
<td>Animal data only</td>
<td>C</td>
</tr>
<tr>
<td>Transforming growth factor α and β [1, 8, 9]</td>
<td></td>
<td>Animal data only</td>
<td>A</td>
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<tr>
<td>Platelet-derived growth factor [1]</td>
<td></td>
<td>Animal data only</td>
<td>C</td>
</tr>
<tr>
<td>Insulin-like growth factor II [1, 10]</td>
<td></td>
<td>Animal data only</td>
<td>B</td>
</tr>
<tr>
<td>Colony stimulating factor-I [1, 11]</td>
<td></td>
<td>Animal data only</td>
<td>B</td>
</tr>
<tr>
<td><strong>Trophoblast proteinases/inhibitors</strong></td>
<td>Regulates trophoblast invasion</td>
<td>Animal data, in-vitro human data</td>
<td>B</td>
</tr>
<tr>
<td>Matrix metalloproteinase-9/tissue inhibitor of metalloproteinase-3 [12–15]</td>
<td>Facilitates trophoblast vascular mimicry</td>
<td>Animal data only</td>
<td>B</td>
</tr>
<tr>
<td>Urokinase-type plasminogen activator/plasminogen activator inhibitor-4 [16]</td>
<td>Regulates trophoblast invasion</td>
<td>Animal data, in-vitro human data</td>
<td>B</td>
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<tr>
<td>Cathepsin B and L [17]</td>
<td></td>
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<tr>
<td><strong>Hormones</strong></td>
<td>Maintains progesterone release from corpus luteum</td>
<td>Animal data, in-vitro and in-vivo human data</td>
<td>A</td>
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<tr>
<td>Human chorionic gonadotrophin [18]</td>
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<tr>
<td><strong>Immunological factors</strong></td>
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<tr>
<td>HLA-G [19–22]</td>
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<td><strong>Adhesion molecule expression</strong></td>
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<tr>
<td>↓ Integrin αβ, E-cadherin [23–25]</td>
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<td></td>
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<tr>
<td>↑ Integrin αβ, -αβ, VE-cadherin [23–25]</td>
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<tr>
<td><strong>Other factors</strong></td>
<td></td>
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<tr>
<td>Prostaglandin E2 [26]</td>
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<td></td>
<td></td>
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<tr>
<td>Platelet-activating factor [1]</td>
<td></td>
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</tbody>
</table>

*This table highlights the most important factors and is not intended to be all inclusive.

*Studies were reviewed, evaluated for quality based on the highest level of evidence found in the data, and graded into the following categories: (A) there is good evidence to support involvement; (B) there is fair evidence to support involvement; (C) there is insufficient objective evidence to support involvement; however, involvement has been suggested by respected authorities or anecdotal (unpublished) data.

Figure 1. Implantation and the maintenance of early human pregnancy. A schematic section through an implanted embryo (about 14 days following conception) illustrating some of the hormones and paracrine/autocrine factors implicated in implantation and trophoblast invasion. Reproduced with permission, from Norwitz et al. (2001). Abbreviations: HCG, human chorionic gonadotrophin; HLA-G, human leukocyte antigen G; VEGF, vascular endothelial growth factor.
spontaneous pregnancy loss (Csapo and Pulkkinnen, 1978). These data suggest that adequate progesterone production by the corpus luteum is critical to the maintenance of pregnancy until the placenta takes over this function at around 7–9 weeks of gestation. The mode of action of progesterone is not well understood, but appears to be partially independent of interaction with either progesterone or glucocorticoid receptors (Schust et al., 1996). It is likely that progesterone acts to decrease endometrial prostaglandin production both directly [by inhibiting the release of arachidonic acid from endometrial cells (Wilson et al., 1986)] and indirectly [by up-regulating inhibitors of prostaglandin synthesis (Norwitz and Wilson, 2000; Norwitz et al., 2006)]. Progesterone may also act by altering prostaglandin receptor activity. Mice deficient in the HOXA-10 gene, for example, have a reproductive phenotype characterized by abnormalities in decidualization and implantation (Benson et al., 1996) that have been linked to aberrations in progesterone-regulated expression of two prostaglandin receptor subtypes, EP3 and EP4, in the uterine stroma (Lim et al., 1999). The presence in the decidua of two endogenous inhibitors of prostaglandin production that may be important in implantation have recently been identified, namely secretory component (Norwitz et al., 2000) and surfactant protein-A (SP-A) (Norwitz et al., 2006).

The rate-limiting step in the synthesis of prostaglandins of the 2-series is the hydrolysis of non-esterified (free) arachidonic acid from membrane phospholipid. This release is mediated by the phospholipase family of enzymes, primarily phospholipase A, (PLA,). In 1985, Wilson et al identified an endogenous inhibitor of PLA, in the amniotic fluid of women in the third trimester of pregnancy, and called this compound ‘gravidin’. Subsequent studies have demonstrated that gravidin is the fetal homologue of adult secretory component (SC) of the polymeric immunoglobulins, IgA and IgM (Wilson et al., 1989; Wilson and Christie, 1991). SC is a 58-kDa glycoprotein that binds to IgA and IgM on the abluminal surface of epithelial glandular cells, transports them across the glands, and is released into the exocrine secretions covalently bound to immunoglobulin. In its unbound (free) form within endometrial glandular cells, however, SC, like gravidin, is able to inhibit PLA, activity (Wilson et al., 1985, 1989; Wilson and Christie, 1991). Both SC and prostaglandin production have been localized primarily to glandular epithelial cells in the decidua, and have shown that progesterone stimulates SC expression in these cells resulting in prostaglandin production by decidual stromal cells in vitro without affecting the production of other inflammatory mediators and angiogenic factors (Norwitz et al., 2006). SP-A appears to exert this effect by binding directly to the cytoplasmic protein, peroxiredoxin 6, which has endogenous PLA, activity (Wu et al., 2006). The role SP-A in implantation has yet to be fully delineated.

**Role of decidual haemorrhage in implantation and placentation**

Decidual haemorrhage (placental abruption) and vaginal bleeding in early pregnancy is associated with adverse pregnancy outcome including spontaneous abortion, preterm labour, pPROM, and pre-eclampsia (Salafia et al., 1995; Aoyama et al., 2003; Nagy et al., 2003; Weiss et al., 2004). Pathological studies have also shown evidence of old bleeding (haemosiderin deposition) in the placentae and fetal membranes of pregnancies complicated by pre-eclampsia and preterm labour (Salafia et al., 1995). Moreover, pre-eclampsia has been linked to inherited and acquired thrombophilias as represented by the factor V Leiden mutation (Alfirevic et al., 2002; Dudding and Attia, 2004; Lin and August, 2005) and antiphospholipid antibody syndrome (Branch et al., 2001) respectively. Taken together, these data suggest that decidual haemorrhage in early pregnancy may impair trophoblast invasion.

Decidua is a rich source of tissue factor (Lockwood et al., 1993, 1994), and decidual cells are in close proximity to invading cytrophoblasts. If decidual haemorrhage occurs, it enables circulating factor VII to bind to decidual cell-expressed tissue factor to generate thrombin, which promotes haemostasis by cleaving fibrinogen to form the fibrin clot. Beyond its haemostatic role, thrombin promotes acute inflammation by binding to protease-activated receptors to induce decidual cells to synthesize and secrete interleukin-8 (IL-8), which attracts neutrophils (Lockwood et al., 2005). Thrombin also promotes chronic inflammation by inducing monocyte/macrophage infiltration via enhanced monocyte chemoattractant protein-1 (MCP-1) expression (Colotta et al., 1994; Grandaliano et al., 1994). The cellular mechanisms by which thrombin may impair trophoblast invasion are not well understood, but likely involves the local production of angiogenic factors at the maternal–fetal interface.

As discussed, the primary defect of pre-eclampsia is shallow trophoblast invasion leading to incomplete vascular transformation and inadequate uteroplacental perfusion. Recent attention has focused on the role of angiogenic factors, in particular vascular endothelial growth factor (VEGF) and placenta growth factor (PIGF), in establishing the definitive uteroplacental circulation. These factors act via specific Flt-1 and KDR surface receptors to regulate angiogenesis and vascular integrity. They are inhibited by binding to soluble fms-like tyrosine kinase-1 (sFlt-1), a splice variant of the VEGF receptor type 1 (Flt-1) that is highly expressed by cytrophoblasts and released into the maternal circulation (Burri et al., 2004). Concentrations of sFlt-1 are elevated in the placentae (Clark et al., 1998; Maynard et al., 2003), serum (Tsatsaris et al., 2003), and urine (Bühnschi et al., 2005) of women with pre-eclampsia, and fall precipitously after delivery of the placenta in concert with resolution of the clinical syndrome. Inhibition of VEGF activity, either by interfering with VEGF binding to...
its functional trans-membrane receptors (Clark et al., 1998) or by sequestering VEGF in the circulation by binding to sFlt-1 (Maynard et al., 2003; Tsatsaris et al., 2003), leads to an inhibition of trophoblast invasion and trophoblast-induced vascular transformation (pseudo-vascularogenesis). It has recently shown that thrombin stimulates sFlt-1 expression by first trimester decidual cells (Lockwood et al., 2006). Thus, decidual haemorrhage and excess thrombin generation in early pregnancy will result in enhanced decidual cell sFlt-1 expression and an imbalance in angiogenic factors at the level of the developing maternal–fetal interface. This suggests the existence of a novel association between decidual haemorrhage the shallow trophoblast invasion of the decidua that leads to pre-eclampsia.

Conclusions

At a functional level, the placenta must integrate maternal and fetal physiology, immunology, and endocrinology. Complications that present relatively late in pregnancy may actually reflect errors that occurred much earlier in placental development. Whether such errors can be detected and corrective action taken before pregnancy outcome is compromised remains uncertain. An improved understanding of the molecular mechanisms responsible for abnormal implantation and placentation will likely improve clinicians’ ability to treat disorders that occur along this continuum, including infertility, recurrent pregnancy loss, pre-eclampsia, and preterm birth.

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Received 22 May 2006; refereed 5 July 2006; accepted 17 July 2006.